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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,578	03/02/2004	David George Putman	R0149B-REG	3091
24372	7590	02/24/2006	EXAMINER BERNHARDT, EMILY B	
ROCHE PALO ALTO LLC PATENT LAW DEPT. M/S A2-250 3431 HILLVIEW AVENUE PALO ALTO, CA 94304			ART UNIT 1624	PAPER NUMBER

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/791,578	Applicant(s) PUTMAN, DAVID GEORGE	
	Examiner Emily Bernhardt	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
 4a) Of the above claim(s) 33-36 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-32 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>3/2/04 & 9/15/04</u> . | 6) <input type="checkbox"/> Other: ____. |

Restriction to one of the following inventions is required under 35 U.S.C.

121:

- I. Claims 1-32, drawn to compounds, compositions where
R5=piperazines (i.e. Z=N and r=2), classified in class 544, subclass
363; class 514 subclass 253.05.
- II. Claims 1-13,17-24,28 and 32, drawn to compounds and compositions
where R5=other rings not provided for by I, classified in classes such
as 540 when 7-membered, class 546 when R5 is 6-membered ,
subclasses various as determined by the exact nature of ring formed;
class 514, various subclasses.
- III. Claims 33-35, drawn to multiple uses employing compounds of I,
classified in class 514, subclass 253.05.
- IV. Claims 33-35, drawn to multiple uses employing compounds of II,
classified in class 514, subclasses various.
- V. Claim 36, drawn to a process for making some of the compounds of I
and II, classified in class 544 and other classes, subclass such as 363
and others.

Whichever Group is elected applicants must further elect a single
species. If II or IV or V is elected applicants must pick a specific R5

ring as was done in I. If III/IV elected applicants must further elect a single use .

The inventions are distinct, each from the other because of the following reasons: Compounds within I and II can vary substantially based on the R5 choices as well as R2 which are separately classified and may raise separate issues of patentability. Note art applied below is pertinent only to small part of Group I subject matter.

Inventions I/II and V are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case more than one process exists for making instant compounds as evidenced at the very least by applicants' alternate schemes presented in the specification as well as those described in Ohkura applied below.

Inventions I/II and III/IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with

another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case more than one use exists for instant compounds as is evident by the many being claimed as well as those described by Ohkura for similar compounds.

During a telephone conversation with Mr. Hall on 1/30/06 a provisional election was made without traverse to prosecute the invention of I, claims 1-32 and in particular species of eg.2. Affirmation of this election must be made by applicant in replying to this Office action. Claims 33-36 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed to a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require

the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The abstract of the disclosure is objected to because it does not describe intended uses for claimed compounds. Correction is required. See MPEP § 608.01(b).

Claims 1-30 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Scope of piperazines claimed is not adequately enabled. From a reading of the specification nature of rings permitted at R2 are mono- and polyfused carbocyclics as well as hetero-containing rings which in turn can be further substituted with a variety of functional groups including “acyl” of nonlimiting scope. The same applies to the scope at R1 which includes “heteroalkyl” where up to 3 hetero-containing moieties can be present which in turn are either alkylated or acylated with “acyl” groups of nonlimiting scope. Compounds made and indicated as tested are much closer to each other than to remaining scope being predominately phenyl or naphthyl with substituents such as

halo, alkyl, CF₃, alkoxy, fewer examples with CONH₂ or NHC(O)NH₂ or S(O)₂Me with the isoquinoline ring system lacking any additional substitution at R₁. Note *In re Surrey* 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art.

Also note the criteria for enablement as set out in *In re Wands* cited in MPEP 2164.01(a), August 2000 edition, which includes factors such as:

1) Breadth of the claims- the claims cover compounds easily in the millions as pointed out above;

2) Level of unpredictability in the art- the invention is pharmaceutical in nature as it involves binding to 5-HT₆ serotonin receptors selectively. It is well established that “the scope of enablement varies inversely with the degree of unpredictability of the factors involved” and physiological activity is generally considered to be unpredictable. See *In re Fisher* 166 USPQ 18;

3) Direction or guidance- the compounds made and presumably tested as described on p.42 of the specification are not representative of the instant scope but are closer to each other than to remaining scope as discussed above;

4) State of the prior art- The compounds are piperazine derivatives which are attached to the isoquinoline ring system at the 5- or 6-positions with the 1-position

sulfonated or alkylated with a variety of rings. While such compounds are known as evident from the art applied below, they are directed to only a small part of applicants' scope and for different uses and thus do not evidence the many structural permutations permitted in the instant scope are known in the prior art for the same activity relied on herein;

5) Working examples- No actual test data has been presented and thus no clear indication of how the many untested functional groups at various positions out of the many claimed might affect potency to a large or small degree.

In view of the above considerations, this rejection is being applied.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3,5,17-19,21,23-28,30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ohkura (WO'135). The WO publication was published on 12/3/98 which is considerably prior to applicants' effective filing date. The examiner is relying on the US equivalent (US'362) provided by applicants as the English translation. Ohkura describes similar compounds to that claimed herein when instant Y is CR^aR^b and $X=C(O)$ for uses based on their lipid-lowering

activity. See isoquinolone species listed in columns 89-96. These species differ in two respects from that claimed herein. The first difference is in the point of attachment of the piperazine ring to the isoquinoline ring system. Ohkura's compounds are attached at the 7- vs. instant 5- or 6- positions. The second difference is in the nature of substitution at the 4-position of the piperazine ring which is exemplified in Ohkura as diphenylmethyl, etc. vs. instant alkyl. However Ohkura teaches attachment at all ring positions of the benzene portion of the ring system and additionally teaches alkyl as a choice at the 4-position of the piperazine ring. See formula (I) in col.2 and definition of "X-Y-Z". Note that 5th last species in claim 31 is thus also an obvious variant. Thus it would have been obvious to one skilled in the art at the time the instant invention was made to expect corresponding position isomers of Ohkura's compounds that are alkylated on piperazine ring to be also useful as lipid-lowering agents in view of the express equivalency teachings outline above.

Claims 14-16 and 25-27 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot refer back to different sets of claims to different features. See MPEP § 608.01(n).

Elected species corresponding to Y as SO₂ is not taught or suggested by the art of record or from a search in the pertinent art area.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Bernhardt whose telephone number is 571-272-0664.

If attempts to reach the examiner by telephone are unsuccessful, the acting supervisor for AU 1624, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.



Emily Bernhardt
Primary Examiner
Art Unit 1624